JOC The Journal of Organic Chemistry

Article

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Aromatic Triazole Foldamers Induced by C−H···X (X = F, Cl) Intramolecular Hydrogen Bonding

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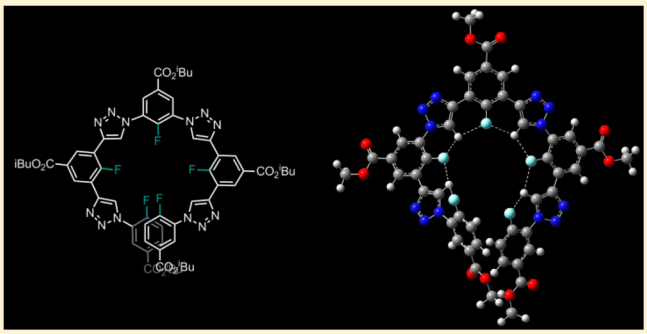
Supporting Information

ABSTRACT: Aryl-triazole oligomers based on isobutyl 4-fluorobenzoate and isobutyl 4-chlorobenzoate were designed and synthesized. Crystal structure and $^{1}H-^{1}H$ NOESY experiments demonstrate that the oligomers adopt stable helical conformation, which are induced by C^{5}−H···X−C (X = F, Cl) intramolecular hydrogen bonding between triazole protons and halogen atoms. The stabilities of the folded conformations are confirmed by DFT calculations, which show that each C^{5}−H···F−C planar interaction lowers the energy by ∼3 kcal mol^{-1} on average, and by ∼1 kcal mol^{-1} when C^{5}−H···Cl−C bridges are formed. The hydrogen-bonding networks are disrupted in competitive hydrogen-bonding media such as DMSO, generating the unfolded oligomers.



INTRODUCTION

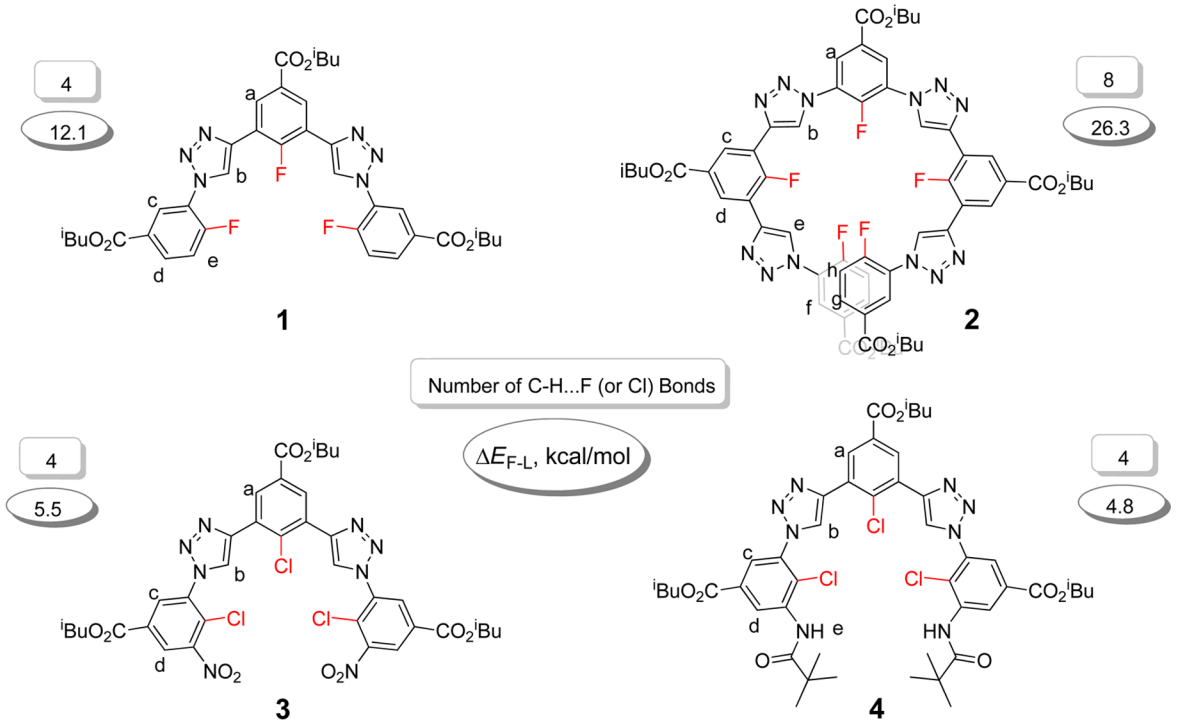
Hydrogen bonding has been widely used in the development of synthetic oligomers which adopt helical conformations, so-called foldamers, to mimic their natural counterparts such as proteins.[1] Initial studies focused mainly on traditional strong hydrogen bonds such as O−H···O, O−H···N, and N−H···O, etc.,[2] and the properties of foldamers utilizing these types of hydrogen bonding is becoming increasingly understood. On the contrary, the construction of foldamers based on weaker hydrogen bridges, whose interaction energies are less than 16 kcal mol^{-1},[3] is less studied. While fluoride and chloride ions are well-known as very strong hydrogen-bond acceptors,[4] covalently bound halogen atoms, in contrast, were considered to hardly ever form hydrogen bonds.[5] In recent years, with increasing importance of organic halogens in medicinal chemistry and chemical biology,[6] the properties of noncovalent halogen interactions have become better understood,[7,8] and the fast progress achieved in this area indicates that the weak interactions such as C−F···H−N (or O) or C−Cl···H−N (or O) can play a crucial role in protein−ligand interaction,[9] reactional stereoselectivity,[10] and supramolecular assembly.[11] In particular, these types of hydrogen bonds have been used in the construction of foldamers, in which halogen−hydrogen bonding is the only driving force for folding.[12] For example, Li and co-workers reported that intramolecular C−F···H−N hydrogen bonds can be utilized to construct 2-fluorobenzamide-based foldamers.[13] Our previous works also demonstrated that fluorine (or chlorine)-substituted oligo(quinoline-amide)s are able to fold into single, double or quanta-helixes driven by the C−F(or Cl)···H−N hydrogen bonding between the fluorines (or chlorines) and adjacent amide protons.[14,15] However, to date there have been no reports on foldamers induced by C−F(or Cl)···H−C bridges, which is probably due to the fact that, in most cases, this kind of bonding is too weak to constrain the main strands of the oligomers.

It is well-known that the strength of a hydrogen bond will increase as the hydrogen atom becomes more electron-deficient. Accordingly, to improve the bonding strength of C−F(or Cl)···H−C, polarization of the H−C bond via substitution on the carbon with very strong electron-withdrawing groups, such as F[16] and CN,[17] is often necessary. In this aspect, the 1,2,3-triazole moiety is one of the recent examples that has shown capability to serve as an excellent hydrogen bond donor due to its high dipole moment (4.55 D in comparison with 1.45−1.70 and 0.92−1.53 D for traditional donors O−H and N−H, respectively) attributed to three sp^{2} hybridized nitrogen atoms. We and other groups previously reported several types of halide-ion-controlled oligo(aryl-1,2,3-triazole)s foldamers, in which the folding was driven by the

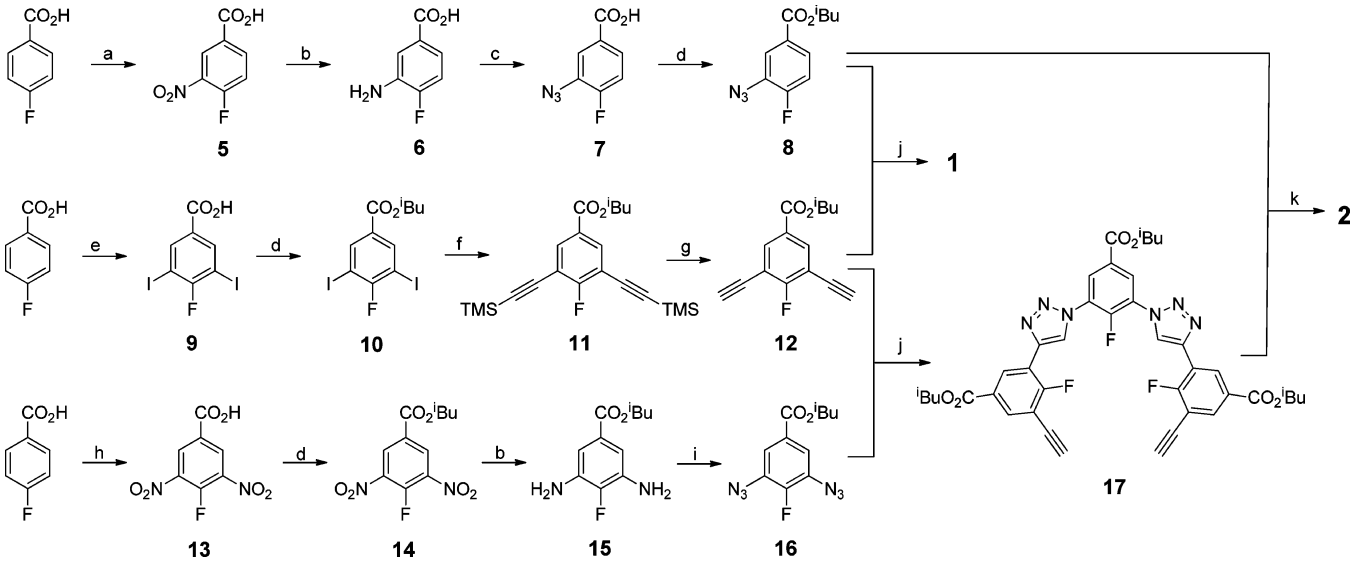
Received: March 25, 2014
Published: May 13, 2014

   dx.doi.org/10.1021/jo500582c | J. Org. Chem. 2014, 79, 5134−5144

Scheme 1. Structure of Oligomers 1−4, Number of C^5−H···F (or Cl) Bonds in Each Oligomer As Well As the Energy Gap (ΔE_{F-L}) between their Folded and Linear (completely unfolded) States Determined Computationally by Density Functional Theory (DFT)



Scheme 2. Synthesis of Fluorine-Substituted Aryl-Triazole Oligomers 1−2[a]



[a]Reagents and conditions: a) KNO_3/H_2SO_4; b) Fe, AcOH; c) HCl, $NaNO_2$; NaN_3; d) oxalyl chloride; *i*-BuOH, *N*-ethyldiisopropylamine; e) H_2SO_4 (90%), CrO_3, I_2; f) CuI, $Pd(PPh_3)_4$, $(iPr)_2NH$, trimethylsilylacetylene; g) $KF{\cdot}2H_2O$; h) fuming HNO_3, fuming H_2SO_4; (i) TFA, *tert*-butyl nitrite; NaN_3; j) $CuSO_4$, L-sodium ascorbate; k) $CuSO_4$, L-sodium ascorbate, tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine.

C^5−H···X (X = F^-, Cl^- or Br^-) bonding.[18,19] More recently, Hecht and Li found that the 1,2,3-triazole−fluorine H-bonding interaction, C^5−H···F−C, can induce rotational constraints of short aryl-triazole backbones.[20] The systems in the solid state have been observed to possess a nearly planar geometry and H···F distances of 2.3−2.9 Å, dependent on the side of fluorine located (i.e., on the side of C^4 or N^1 of the triazole). If the triazole has a fluorine acceptor interacting from both sides, the hydrogen-bonding interaction was averaged, providing an identical H···F distance of 2.45 Å.[20b] These findings provide a hope to utilize this type of binding motif to develop new types of foldamers. However, when one considers the increased steric interactions and the other possible intrachain interactions such as electrostatic or dipole repulsion originating from the fluorines and triazoles present in the folded conformation of oligomers incorporating multiple motifs, the folding of such oligomers may not be thermodynamically favorable. Indeed, the

dx.doi.org/10.1021/jo500582c | J. Org. Chem. 2014, 79, 5134−5144

foldability of longer oligomers incorporating halogen aryl-triazole units until now has not been established yet.

In this contribution, we report the synthesis of the aromatic triazole oligomers **1**−**4** (Scheme 1) based on isobutyl-4-fluorobenzoate or isobutyl-4-chlorobenzoate and the characterization of their folded conformations. Also, to theoretically confirm the foldability of the oligomers **1**−**4**, their global minimum energy conformations, as well as the energy levels for various unfolded conformations were calculated using density functional theory (DFT).

RESULTS AND DISCUSSION

Synthesis. Synthetic routes for compounds **1** and **2** are outlined in Scheme 2. Starting from 4-fluorobenzoic acid, aromatic nitration with a mixture of potassium nitrate and sulfuric acid or fuming nitric acid and fuming sulfuric acid provided mono and dinitro-compound **5** and **13**, respectively. Reduction of **5** with iron powder gave **6**. Diazotization of **6** in the presence of NaN_3 provided **7**, which was further converted to the acid chloride by oxalyl chloride with DMF as a catalyst and then reacted with *i*BuOH to generate monoazido-benzoic ester **8**. To prepare diazido-benzoic ester, compound **13** was at first converted to the acid chloride with oxalyl chloride and DMF then esterified to give **14**. Although the same condition was used for this reaction as that for preparation of **8**, it was observed that compound **13** was easier to convert to the corresponding acid chloride in comparison with the case of **7**, which was probably due to the enhancement of electrophilicity of the carbonyl group attributed to two nitro groups in comparison with that for **7**. Compound **14** was very easy to hydrolyze so that the crude compound was directly reduced by iron powder to generate **15**. Due to the limited solubility of **15** and the instability of the diazo salt in water, diazotization of **15** using trifluoroacetic acid and *tert*-butyl nitrite in tetrahydrofuran, followed by dediazotization with the help of sodium azide, provides diazido-benzoic ester **16**. On the other hand, iodination of 4-fluorobenzoic acid using iodine and chromium-(VI) oxide in the acidic anhydrous medium gave **9**, which was further esterified to yield **10**. Sonogashira coupling of **10** with trimethylsilylacetylene, followed by removal of the TMS group under basic condition, provides **12**. Thus, through the "Click" coupling of **8** and **16** with **12**, respectively, aryl-triazole oligomers **1** and **2** were prepared.

Fluorine-substituted oligo(aryl-triazole)s foldamers. The crystal structure of **1** (Figure 1, left) obtained by slowly evaporating the solvent of mixture of dichloromethane and ethanol showed a crescent coplanar arrangement of the whole aryl-triazoles main strand. The dihedral angles between the adjacent triazole and benzene ring are all less than 17°, and the distance between the triazole protons and the neighboring fluorine atoms is 2.3−2.4 Å (Table 1), indicating a nearly planar, folded conformation with a strong intramolecular C^5−H···F−C hydrogen-bonding network. The DFT optimization also gives rise to a crescent structure of oligomer **1** (Figure 1, right), with the predicted peripheral torsion angles a little bit larger than the ones in the crystal structure (Table 1). Although crystal structure geometry may not always represent the true ground-state conformations for a monodisperse molecule due to intermolecular interactions and solvation effects, the optimized geometries still bear a close resemblance to the single-crystal geometry in this case.

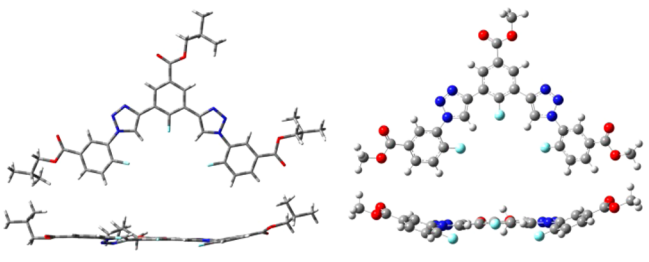


Figure 1. Crystal structures of compound **1** (left) as well as its energy-minimized geometry calculated at the DFT RB3LYP 6-31 G(d,p) level (right) within the Gaussian 09 software package.[21]

Table 1. Parameters of the Crystal Structures of 1 and 4 As Well As the Energy-Minimized Structures of 1−4 Calculated at the DFT RB3LYP/6-31G(d,p) Level[a]

oligomer	θ [b] (°)	d [c] (Å)	d_{avg} [d] (Å)	φ [e] (°)
1 (expt)	12, 2, 17, 15	2.3–2.4	2.35	15, 0, 18, 18
1 (DFT)	26, 0, 0, 26	2.3–2.4	2.33	31, 0, 0, 31
2 (DFT)	41, 15, 36, 6, 9, 23, 3, 24	2.3–2.5	2.37	48, 18, 45, 7, 10, 28, 4, 29,
3 (DFT)	54, 26, 23, 51	2.7-2.9	2.80	60, 28, 26, 62
4 (expt)	52, 19, 30, 46	2.5–2.9	2.69	17, 54, 34, 26, 54, 33
4 (DFT)	56, 24, 26, 58	2.4–3.0	2.70	0, 66, 27, 26, 66, 0

[a]The angle and distance discussed in this table are illustrated in Figure 2. [b]The dihedral angles between triazole and the adjacent benzene ring in the strand listed in sequence. [c]The range of H···X (X = F or Cl) distances. [d]The average H···X (X = F or Cl) distances. [e]The bond angles of the C^5−H···X (X = F or Cl) hydrogen bonds listed in sequence.

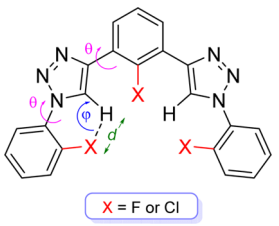


Figure 2. Model for elaboration the structural parameters.

The ^{1}H NMR spectrum of **1** in $CDCl_3$ showed one set of sharp signals with chemical shifts independent of the concentration in the range of 0.3−10 mM, indicative of no aggregation taking place (Figure S2, Supporting Information [SI]). The signal of triazole protons H_b splits into a triplet (Figure 3) with the coupling constant of 3.0 Hz. The splitting of the H_b proton is due to the coupling from two neighboring fluorine atoms, in agreement with the observation from Li, et al. on the fluorine substituted 1,4-diaryl-1,2,3-triazoles.[20] Since the $^5J_{HF}$ coupling, in most cases in nonstrained compounds, has a magnitude of less than 0.5 Hz which is usually resolved in ^{1}H NMR spectrum, the remarkable coupling in this case should be produced through the intramolecular triazole-proton-centered hydrogen-bonding framework, C^5−H···$(F-C)_2$. This kind of "through-space" coupling was also confirmed by the disappearance of its triplet pattern upon dissolving into DMSO-d_6 (Figure S1, SI). This disappearance was due to competition with the better hydrogen-bond donor DMSO, leading to collapse of the intramolecular hydrogen-bonding network of the foldamer. In the ^{1}H−^{1}H NOESY spectrum of **1** in $CDCl_3$,

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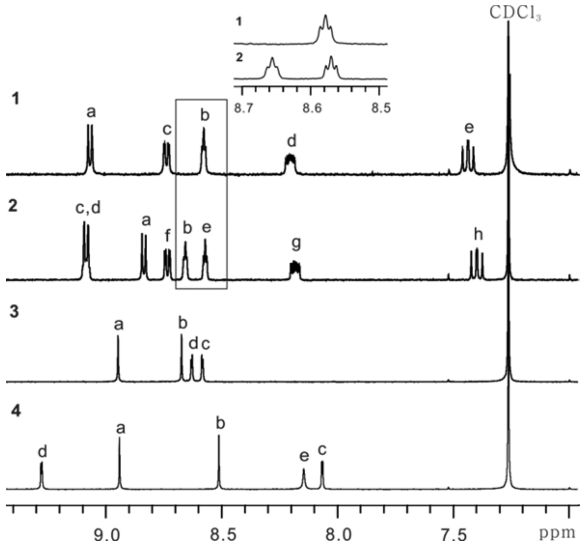


Figure 3. Partial ^{1}H NMR spectra (400 MHz, 298 K) of oligomers **1**−**4** in $CDCl_3$. The inset plots on the top correspond to the signals of triazoles on **1** and **2**. [**1**] = [**2**] = [**3**] = [**4**] = 2 mM.

the correlation between the triazole proton and the adjacent *o*-phenyl proton (H_b and H_a) was not observed (Figure S4, SI), suggesting the dynamic rotation of the molecules through two carbon−nitrogen linkages between the benzene rings and the triazole were restricted by the intramolecular C^5−H···F−C bonding. The stability of the folded conformation of **1** is supported by DFT results, which predicts oligomer **1** to possess a folded conformation that is about ∼12 kcal mol^{-1} lower in energy than the unfolded one (Figure S14, SI).

The folded conformation of **2** in $CDCl_3$ was first confirmed by ^{1}H NMR spectroscopic analysis. Upon dilution from 14 mM to 0.4 mM, the chemical shifts of triazole protons in the ^{1}H NMR spectra of **2** in $CDCl_3$ displayed no significant changes (Figure S3, SI), indicating that the intermolecular interactions were weak in this range of concentration. In addition, the splitting pattern of triazole protons could clearly be observed which showed triplets for both H_b and H_e with J_{HF} = 2.8 and 3.0 Hz, respectively (Figure 3). The spin−spin coupling constant of H_b is slightly smaller than that of H_e, which is probably due to the fact that the central fluorine is more sterically hindered because of the folding of **2**, resulting in more steric deshielding of the central fluorine.[22] This affects the coupling to the relative triazole protons. In the corresponding 2D NOESY spectrum of **2**, the cross-peaks between the triazole protons and the *o*-phenyl protons are completely absent (Figure 4, left), providing additional evidence for the helical conformation of **2**. Unfortunately, compound **2** is not soluble in DMSO. In 1:2 (v/v) $CDCl_3$/DMSO-d_6, the ^{1}H NMR spectra of **2** showed no splitting for the signals of triazoles protons H_b and H_e due to the disruption of the hydrogen-bonding network by DMSO (Figure 5). Furthermore, under such conditions, a

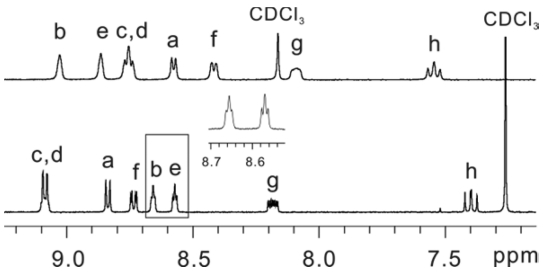


Figure 5. Partial ^{1}H NMR spectra (400 MHz, 298 K) of compound **2** in $CDCl_3$ (bottom) and $CDCl_3$/DMSO-d_6 = 1:2 (v/v) (top) at ambient temperature. The inset plot in the middle corresponds to the signals of triazoles on **2**. [**2**] = 2 mM.

strong NOE correlation of H_b−H_a and comparatively weaker correlations of H_b−H_c, H_e−H_d and H_e−H_f could be observed (Figure 4, right), suggesting that oligomer **2** did not possess folded conformation in DMSO. These observations once again demonstrate that, in $CDCl_3$, the folding of the oligomers was driven by intramolecular C^5−H···F−C bonding.

Since DFT describes the single-crystal geometries of **1** reasonably well, we then applied DFT to explore the ground-state geometry of **2**, for which a single crystal could not be

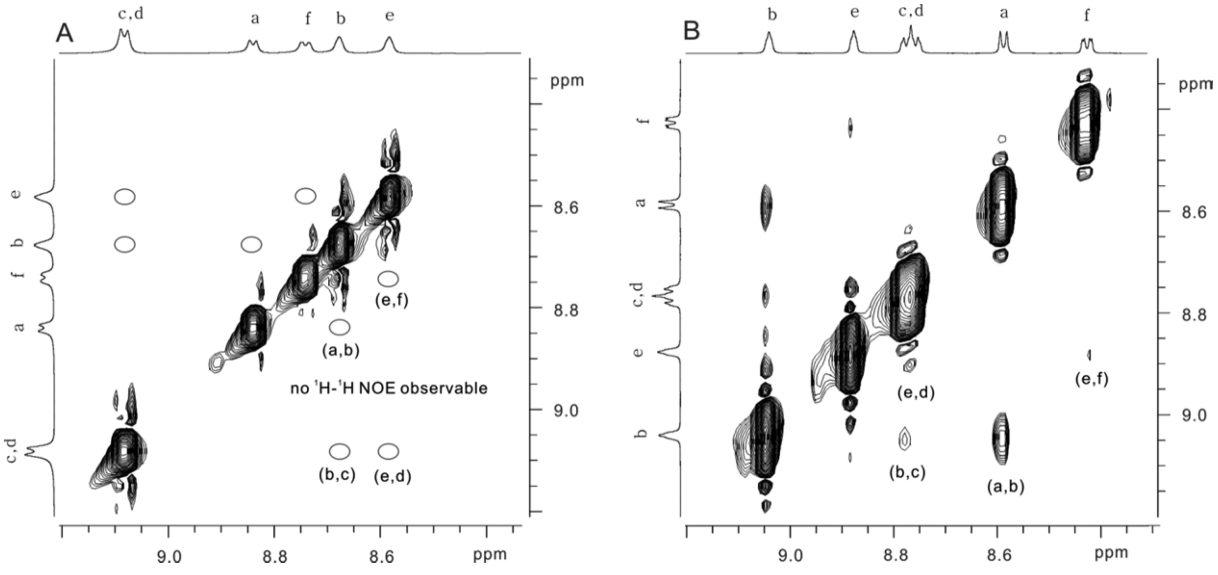


Figure 4. Partial ^{1}H−^{1}H NOESY spectra (500 MHz, 298 K) of oligomer **2** (A) in $CDCl_3$ ([**2**] = 14 mM) and (B) in 1:2 (v/v) $CDCl_3$/DMSO-d_6 ([**2**] = 2 mM).

dx.doi.org/10.1021/jo500582c | J. Org. Chem. 2014, 79, 5134−5144

obtained. The energy-minimized geometry as well as its parameters of oligomer **2** are shown in Figure 6 and Table 1,

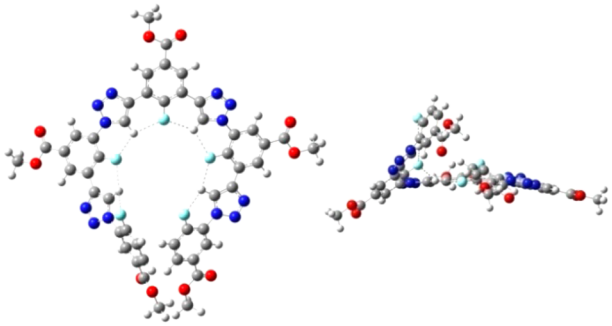
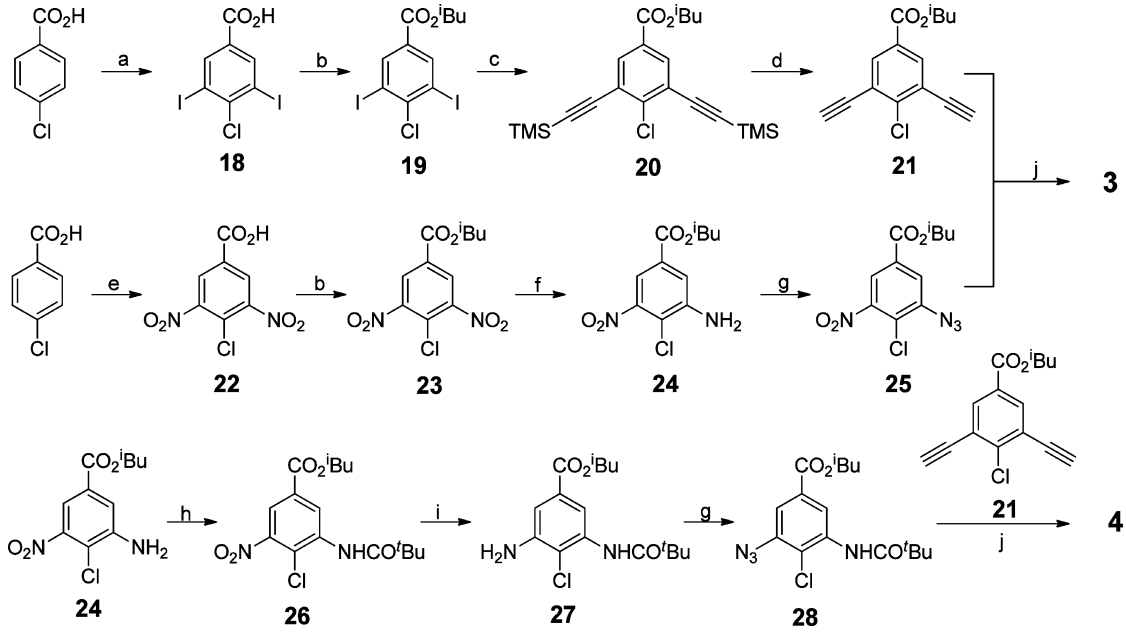


Figure 6. Overhead (left) and side view (right) of lowest-energy geometry of **2** (DFT RB3LYP 6-31 G (d,p)). Methyl groups were substituted for long alky chains for computational efficiency.

respectively. The geometry is a global minimum (confirmed by vibrational analysis as well as comparison with other unfolded minima) in which the core region (i.e., the central fragment containng a phenyl ring and two triazole units) maintains a folded, nearly planar geometry. Closer to the termini of the oligomer, one strand maintains a more planar geometry with the dihedral angles between the adjacent rings of 6−24° while the other is significantly more twisted (dihedral angles between 15−41°) to accommodate sterics (Figure 6, right; Table 1). The C^5−H···F−C hydrogen bond lengths range between 2.3 and 2.5 Å, consistent with the presence of a hydrogen-bonding network.

Oligomer **2** exhibits a continual increase in energy as the degree of unfolding increases. The energy level of the ground-state conformation, which possesses eight C^5−H···F interactions is 11−13 kcal mol^{-1} lower in energy than that of the multiple unfolded minima which possess four C^5−H···F interactions, and lies ∼26 kcal mol^{-1} lower than that of the completely unfolded one (Figure S14, SI). This is markedly different from the system of oligo(phenyl triazole)s without fluorines in which the energy level of the folded conformation is +2.3 kcal mol^{-1} higher than the linear one (by MM2),[23] illustrating the important role of fluorine hydrogen bonding in stabilizing the folding of **2**. Since the stability of the folded conformation for a specified foldamer is determined by the energy gap between its folded and unfolded states, the gap in this case suggests that oligomer **2** has a strong preference to exist in a helical conformation. We also examined two different conformational minima of **2** which possess only four C^5−H···F interactions, one in which the edges are unfolded (*anti*−*syn*−*syn*−*anti*[20a,24]), and another in which the core is unfolded (*syn*−*anti*−*anti*−*syn*) (Figure S14, SI). The results show that these conformations are nearly degenerate, with the former being only 1.5 kcal mol^{-1} lower in energy, which is probably due to the greater alleviation of steric strain in unfolding the edges or increased conjugation in the case of *anti*−*syn*−*syn*−*anti* conformer. Our DFT results suggest that each C^5−H···F−C planar interaction lowers the energy by ∼3 kcal mol^{-1} on average, which was obtained by dividing ΔE_{F-L} by the number of C^5−H···F (or Cl) bonds (Figure 1 and Figure S14 in the SI). This is consistent with the gap between the folded and completely unfolded conformation of **1** (12.1 kcal mol^{-1}, four C^5−H···F interactions), but less than the predicted energy difference between the *syn* and *anti* conformations of the model motif, (*o*-fluorophenyl) triazole[20a] (6.4 kcal mol^{-1} or 4.7 kcal mol^{-1}, depending on whether the phenyl is connected at the N^1 or C^4 of the triazole). The diminished gap in our case could arise from the increased electrostatic repulsion of the additional fluorine units as well as the bigger steric hindrance from the longer oligomer strand, which slightly destabilizes the folded conformations. However, the positive value of ΔE_{F-L} indicates

Scheme 3. Synthesis of Chlorine-Substituted Aryl-Triazole Oligomers 3, 4[a]



[a]Reagents and conditions: a) H_2SO_4 (90%), CrO_3, I_2; b) oxalyl chloride, *i*-BuOH, *N*-ethyldiisopropylamine; c) CuI, $Pd(PPh_3)_4$, $(i\text{-Pr})_2NH$, trimethylsilylacetylene; d) $KF{\cdot}2H_2O$; e) KNO_3/H_2SO_4; f) Fe, AcOH; g) HCl, $NaNO_2$; NaN_3; h) *N*-ethyldiisopropylamine, *t*-BuCOCl; (i) Pd/C, H_2; j) $CuSO_4$, L-sodium ascorbate.

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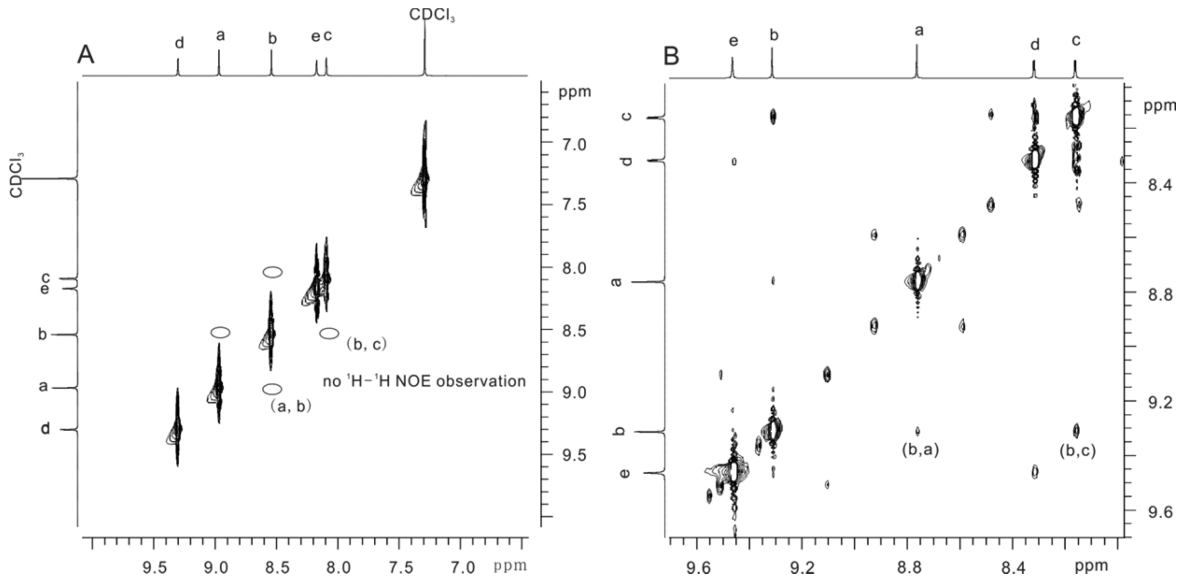

Figure 7. Partial $^1H-^1H$ NOESY spectra of oligomer **4** in (A) $CDCl_3$ (600 MHz, 298 K; [**4**] = 8 mM) and (B) DMSO-d_6 (500 MHz, 298 K; [**4**] = 4 mM).

that, in these oligomeric systems, the total effect of energetic interactions which are favorable to folding, such as intramolecular $C^5-H\cdots F-C$ bonding and dipole−dipole interactions between the triazole and adjacent fluoro-benzene units, outweigh those which are unfavorable to folding, such as the electrostatic repulsion between fluorine lone pairs as well as steric interactions of the folded oligomer strand.

Because DFT predicted each $C^5-H\cdots F-C$ planar interaction to lower the energy by ∼3 kcal mol, to attempt to see unfolded conformations we employed variable-temperature ^1H NMR for oligomers **1** and **2** in 1,1,2,2-tetrachloroethane-d_2, a solvent that has polarity similar to that of $CDCl_3$ but with a higher boiling point. (Figures S15, S16 in the SI). Besides a diminution of signal intensity at higher temperatures, which was expected due to lowered occupation of the lowest Zeeman energy level, the signal of triazole protons for **1** and **2** do not show considerable changes ($\Delta\delta$ = 0.04 and 0.03 ppm for triazole proton H_b in **1** and **2**, respectively). Since the energy required to break one hydrogen bond is on average only ∼3 kcal mol^{-1}, there should be only a little temperature dependence of the equilibrium between folded and unfolded conformations (by the Van't Hoff equation), i.e., the relative concentrations of folded/unfolded conformations are not drastically altered as temperature increases. On the other hand, the cores of the oligomers likely possess a higher barrier to rotation due to steric interactions, and consequently conformations of the oligomers that involve unfolding of the core may not be accessible even at higher temperatures, providing a possible explanation of why the peaks do not shift much as the temperature increases.

Chlorine-Substituted Oligo(aryl-triazole)s Foldamers. To address the folding of oligo(aryl-triazole)s directed by $C^5-H\cdots Cl-C$ hydrogen bonds in solution, chlorine-substituted aryl-triazole oligomers **3** and **4** were obtained by approaches similar to that for compound **1** (Scheme 3). The structure of oligomer **4** is very similar to that of structure **3**, except the nitro groups of **3** are substituted with *N-tert*-butylamide groups. Since the localized dipoles of the nitro groups of **3** might affect the crystal packing due to strong intermolecular interactions, the substitution of *N-tert*-butylamides was designed to provide us a better chance to obtain the crystal structure of chlorine-substituted aryl-triazole oligomers. After having obtained the compounds, we then performed ^1H NMR and NOESY experiments on oligomers **3** and **4**. As expected, in the ^1H NMR spectra of **3** and **4** in $CDCl_3$, the signal of triazoles are singlets (Figure 3), which does not provide any information on the H-bonding between the chlorines and the triazole protons. However, in the corresponding NOESY spectra, no cross-peaks between the triazole protons H_b and their neighboring aromatic protons H_a and H_c could be observed for both **3** and **4** (Figure 7A and Figure S9 in the SI), which is the same as that in the cases of fluorine-substituted oligomers, indicating **3** and **4** adopt helical conformations in $CDCl_3$. To illustrate the driving force of the folding, $^1H-^1H$ NOESY experiment was performed on **4** in DMSO-d_6, which shows that clear NOE cross-peaks of H_a-H_b and H_b-H_e can be observed (Figure 7B), providing a proof that the folding of oligo(aryl-triazole)s in $CDCl_3$ is driven by $C^5-H\cdots Cl-C$ hydrogen bonding.

Although various methods for growing single crystal of **3** were failed, the single crystal of **4** was successfully obtained by diffusion of *n*-heptane into the solution of **4** in dichlomethane. The solid structure of **4** shows a helical conformation, where the five rings are slightly twisted and tilted up and down in an alternating sequence which provides slightly diminished planarity compared to that of **1** (Figure 8). The difference in geometry is probably due to the larger size of chlorine atoms and longer C−Cl bond length, which increases electrostatic repulsion for a planar geometry, as well as the weaker hydrogen bonds formed with chlorine. The DFT geometry of **3** and **4** in the lowest energy conformation show similar arrangement of the main strands (Figure 8, Table 1 and Figure S14 in the SI). In addition, oligomers **3** and **4** exhibit lower energy gaps between their folded and unfolded conformations (about 5.5 and 4.8 kcal mol^{-1}, respectively). From these DFT results, we estimate that each $C^5-H\cdots Cl$ interaction lowers the energy by only ∼1 kcal mol^{-1} on average, in contrast to the $C^5-H\cdots F$ interaction which lowers the energy by ∼3 kcal mol^{-1}. This result indicates that chlorine-substituted oligo(aryl-triazole)s foldamers are comparatively less stable due to the weaker $C^5-H\cdots Cl-C$ bridge. The DFT calculation predicted the distance between the triazole protons and the neighboring chlorine

dx.doi.org/10.1021/jo500582c | J. Org. Chem. 2014, 79, 5134−5144

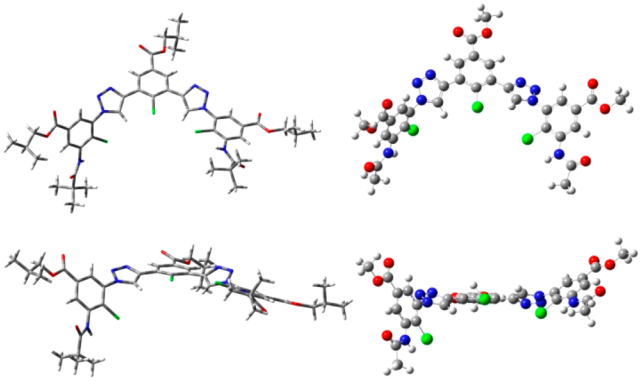

Figure 8. Crystal structure of compound **4** (left) as well as its energy-minimized geometry calculated at the DFT RB3LYP 6-31 G(d,p) level (right).

atoms to be 2.7−2.9 Å for oligomer **3**, and very similar lengths were predicted for **4** (2.4−3.0 Å) (Table 1). Because the DFT-optimized geometry of **4** closely resembles the single crystal geometry, these results suggest that hydrogen bonding between the amide and chlorine of **4** does not significantly affect the C^5−H···Cl bonds; thus **4** provides another analogue to chlorine-substituted aryl-triazole oligomers.

Variable-temperature ^{1}H NMR experiment was also applied to oligomer **4** (Figure S17 in SI). Similar to fluoro-substituted triazole oligomers **1**−**2**, peaks representing triazole protons of chloro-substituted oligomer **4** display no appreciable changes up to 328 K, again indicating a little temperature dependence of the equilibrium due to the relatively low gaps between unfolded/folded conformations and possible barrier to rotation.

CONCLUSIONS

In summary, we have shown that fluorine- and chlorine-substituted oligo(phenyl-triazole)s can fold into helical conformation which is directed by the intramolecular C^5−H···F−C or C^5−H···Cl−C hydrogen-bonding bridges. DFT calculations show that there are large energy gaps between their folded and unfolded states, which determine their strong, well-defined, conformational preferences. These results give a broader insight into the roles of hydrogen bonding between covalently bound halogen atoms and hydrogen attached to carbon in the construction of biomolecules by nature.

EXPERIMENTAL SECTION

All starting materials and common solvents were commercially available and used without further purification unless otherwise noted. Anhydrous tetrahydrofuran (THF) was dried from sodium/benzophenone and then distilled under inert atmosphere. Diisopropylamine (*iso*-Pr_2NH) and DCM were distilled over CaH_2 under argon. Routine NMR spectra were recorded with spectrometers at 400, 500, or 600 MHz (^{1}H NMR). Chemical shifts are reported in δ values relative to the solvent (^{1}H δ ($CHCl_3$) = 7.26 ppm, δ (CH_3SOCH_3) = 2.50 ppm, δ (CH_3COCH_3) = 2.05 ppm, δ (CH_3OH) = 3.31 ppm, δ (CH_3CN) = 1.94 ppm, ^{13}C δ ($CHCl_3$) = 77.16 ppm, δ (CH_3SOCH_3) = 39.52 ppm, δ (CH_3COCH_3) = 29.84, 206.26 ppm, δ (CH_3OH) = 49.00 ppm) peak. Exact mass spectra (EI, ESI, MALDI) were acquired on GCT, FT-ICR spectrometer. IR spectra were recorded on FT-IR spectrometer with thin KBr disk.

3-Nitro-4-fluorobenzoic Acid (5). It was prepared according to a similar procedure described in the literature.[25a] To a solution of 4-fluorobenzoic acid (5.6 g, 40.0 mmol) in concentrated H_2SO_4 (50 mL) in an ice bath was added potassium nitrate (4.4 g, 44.0 mmol) in portions within 30 min. The ice bath was removed and the mixture was stirred at ambient temperature overnight. To the mixture was added crushed ice (500 g) with constant stirring. It took 2 h to melt all the ice at room teperature, the mixture was filtered by a vacuum. The solid was washed with cold water, then dried under vacuum at 50 °C to yield product **5** (4.94 g, 67%) as a light -yellow solid, R_f = 0.3 (DCM/MeOH = 20/4). Mp = 125−127 °C (lit.,[25b] 119−120 °C); ^{1}H NMR (CD_3COCD_3, 400 MHz, 298 K), δ = 8.70 (dd, J = 2.0, 7.2 Hz, 1H), 8.44−8.40 (m, 1H), 7.67 (dd, J = 8.8, 10.8 Hz, 1H); ^{13}C NMR (CD_3COCD_3, 100 MHz, 298 K), δ = 165.0, 160.1, 157.4, 137.84, 137.74, 128.68, 128.64, 128.46, 128.44, 120.01, 119.79; HRMS (ESI-FT-ICR) m/z: [M − H]$^-$ calcd for $C_7H_3FNO_4$ 184.0041; found 184.0046.

3-Amino-4-fluorobenzoic Acid (6). To compound **5** (2.10 g, 11.3 mmol) in the mixture of glacial acetic acid (40 mL) and methanol (40 mL), was added iron powder (2.54 g, 45.3 mmol) at 60 °C, and the mixture was heated to reflux for 4 h. When cooled down to ambient temperature, the mixture was poured into water and extracted with ethyl acetate (30 mL × 5). The combined organic layers were washed with brine (150 mL × 4), dried over Na_2SO_4, and filtered. Solvents were rotary evaporated from the filtrate, and the residue was dried under vacuum to give **6** (1.61 g, 91%) as a pale solid which was used without further purification, R_f = 0.5 (DCM/MeOH = 20/4). Mp = 188−190 °C (lit.,[26] 182−183 °C); ^{1}H NMR (CD_3SOCD_3, 400 MHz, 298 K), δ = 12.66 (s, 1H), 7.40 (dd, J = 2.0, 9.2 Hz, 1H), 7.13−7.09 (m, 1H), 7.05 (dd, J = 8.4, 10.8 Hz, 1H), 5.36 (s, 2H); ^{13}C NMR (CD_3OD, 100 MHz, 298 K), δ = 169.6, 157.0, 154.5, 137.13, 137.0, 128.2, 120.85, 120.77, 119.46, 119.40, 115.88, 115.69. HRMS (ESI-FT-ICR) m/z: [M − H]$^-$ calcd for $C_7H_5FNO_2$ 154.0304; found 154.0300.

3-Azido-4-fluorobenzoic Acid (7). Compound **6** (1.55 g, 10.0 mmol) was dissolved in HCl (18%, 100 mL), and the solution was allowed to cool to 0 °C with ice/salt bath. The solution of $NaNO_2$ (1.04 g, 15.0 mmol) in H_2O (5 mL) was added slowly. After stirring at 0−5 °C for 30 min, a solution of sodium azide (1.95 g, 30.0 mmol) in H_2O (10 mL) was added slowly. The mixture was stirred at room temperature for another 2 h and then was extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (100 mL × 2), dried over Na_2SO_4, and filtered. The solvents were removed, and the residue was dried under vacuum to yield **7** (1.77 g, 97%) as a white solid which was used without further purification, R_f = 0.6 (DCM/MeOH = 20/4). Mp = 158−160 °C, (lit.,[27] 156−167 °C); IR (KBr): 3432 (OH), 3071, 2964, 2656, 2531, 2132 (N_3), 1707 (C═O), 1609, 1587, 1507, 1434, 1330, 1289, 1255, 1232, 1145, 1122, 1086, 1010, 916, 847, 764, 699, 628, 566, 512 cm^{-1}; ^{1}H NMR (CD_3SOCD_3, 400 MHz, 298 K), δ = 13.31 (s, 1H), 7.78−7.72 (m, 2H), 7.44 (dd, J_1 = 8.4 Hz, 10.8 Hz, 1H); ^{13}C NMR (CD_3COCD_3, 100 MHz, 298 K), δ = 166.0, 159.4, 156.9, 129.29, 129.18, 128.89, 128.70, 128.61, 123.49, 123.47, 117.84, 117.64; HRMS (ESI-FT-ICR) m/z: [M − H]$^-$ calcd for $C_7H_3FN_3O_2$ 180.0209; found 180.0204.

Isobutyl 3-Azido-4-fluorobenzoate (8). To compound **7** (1.60 g, 8.84 mmol) suspended in DCM (30 mL, dry) under argon were added oxalyl dichloride (1.70 mL, 20.0 mmol) and DMF (0.1 mL). After stirring at room temperature for 4 h, the solvent and surplus oxalyl dichloride were removed under vacuum to yield acid chloride. The acid chloride was dried by vacuum for 2 h. To a solution of isobutanol (0.92 mL, 10.0 mmol) in DCM (40 mL) containing *N*-ethyldiisopropylamine (1.7 mL, 10.0 mmol), was added the solution of acide chloride in DCM (40 mL) at 0 °C under Ar. The reaction was warmed up to room temperature and stirred overnight. The solvents were evaporated, and the product was purified by flash chromatography (SiO_2, DCM/PE: gradient 1/20 to 1/2) to provide **8** (1.02 g, 49%) as a brown oil, R_f = 0.5 (DCM/PE = 1/2). IR (KBr): 2965, 2877, 2123 (N_3), 1724 (C═O), 1604, 1506, 1469, 1420, 1376, 1310, 1274, 1143, 1109, 1087, 989, 947, 894, 834, 808, 762, 707, 652, 629, 528 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 7.82−7.77 (m, 2H), 7.15 (dd, J = 8.4, 10.4 Hz, 1H), 4.1 (d, J = 6.8 Hz, 2H), 2.09−2.04 (m, 1H), 1.02 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K), δ = 165.04, 158.9, 156.4, 128.61, 128.50, 127.87, 127.83, 127.57, 127.49, 122.73, 122.71, 116.96, 116.76, 71.6, 28.0, 19.3;

dx.doi.org/10.1021/jo500582c | J. Org. Chem. 2014, 79, 5134−5144

HRMS (ESI-FT-ICR) m/z: $[M + Na]^+$ calcd for $C_{11}H_{12}FN_3O_2Na$ 260.0811; found 260.0812.

3,5-Diiodo-4-fluorobenzoic Acid (9). According to literature,[28a] to finely powdered iodine (5.08 g, 20.0 mmol) suspended in H_2SO_4 (90%, 100 mL V/V) was added CrO_3 (2.0 g, 20.0 mmol). The mixture was stirred at about 30 °C for 30 min. To the solution was added 4-fluorobenzoic acid (2.10 g, 15.0 mmol). The mixture was stirred at 25−30 °C for 24 h and then poured into ice/water and filtered by a vacuum. The solid was washed with cool water and then dried by vacuum at 50 °C to give crude **9** (3.65 g, 62%) as a white solid which was used without further purification, R_f = 0.3 (DCM/MeOH = 20/3). Mp = 264−266 °C (lit.[28b] 235−237 °C); ^{1}H NMR (CD_3SOCD_3, 400 MHz, 298 K), δ = 13.47 (s, 1H), 8.27 (d, J = 5.6 Hz, 2H); ^{13}C NMR (CD_3SOCD_3, 100 MHz, 298 K), δ = 164.08, 163.83, 161.4, 140.35, 140.32, 130.31, 130.27, 82.33, 82.03; MS (ESI) m/z: $[M - H]^-$ calcd for $C_7H_2FI_2O_2$ 390.8; found 390.8.

Isobutyl 3,5-Diiodo-4-fluorobenzoate (10). Compound **10** was obtained by a procedure similar to that for compound **8** starting with compound **9**. Yield 89%, white solid, R_f = 0.6 (DCM/PE = 1/2). Mp = 61−63 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 8.38 (d, J = 5.6 Hz, 2H), 4.1 (d, J = 6.8 Hz, 2H), 2.13−2.03 (m, 1H), 1.01 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K), δ = 164.3, 163.1, 161.8, 141.13, 141.12, 129.71, 129.67, 80.47, 80.18, 71.9, 27.9, 19.3; HRMS (EI-TOF) m/z: [M] calcd for $C_{11}H_{11}FI_2O_2$ 447.8832; found 447.8837.

Isobutyl 3,5-Ditrimethylsilylethynyl-4-fluorobenzoate (11). Compound **10** (6.0 g, 13.4 mmol), $Pd(PPh_3)_4$ (0.15 g, 0.13 mmol), and CuI (52 mg, 0.27 mmol) were dissolved in dry THF (100 mL) under Ar. To the solution were added diisopropylamine (10 mL) and trimethylsilylacetylene (4.20 mL, 32.16 mmol). The mixture was stirred at 55 °C overnight. It was filtered, the solvent was removed under reduced pressure, and the residue was redissolved in DCM (100 mL). The solution was washed with saturated NH_4Cl (50 mL × 2) and brine (100 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, DCM/PE: gradient 1/20 to 1/2) to provide **11** (4.57 g, 88%) as a slightly yellow solid, R_f = 0.5 (DCM/PE = 1/2). Mp = 76−77 °C; IR (KBr): 3075, 2962, 2902, 2162 (C≡C), 1725 (C═O), 1597, 1457, 1415, 1396, 1379, 1346, 1327, 1249, 1223, 1102, 1042, 1009, 994, 945, 909, 846, 764, 747, 704, 651 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 8.05 (d, J = 6.4 Hz, 2H), 4.1 (d, J = 6.8 Hz, 2H), 2.12−2.05 (m, 1H), 1.02 (d, J = 6.8 Hz, 6H), 0.26 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K), δ = 167.2, 164.6, 135.1, 126.61, 126.57, 112.82, 112.65, 102.2, 96.2, 71.69, 28.0, 19.3, −0.1; HRMS (ESI-FT-ICR) m/z: $[M + H]^+$ calcd for $C_{21}H_{30}FO_2Si_2$ 389.1768; found 389.1770.

Isobutyl 3,5-Diethynyl-4-fluorobenzoate (12). To compound **11** (4.50 g, 11.60 mmol) which was dissolved in THF (40 mL) and methanol (40 mL) was added KF·2H$_2$O (5.45 g, 58.0 mmol). It was monitored by TLC, and after stirring at room temperature for 4 h, the reaction mixture was concentrated under reduced presure. To the residue was added water (100 mL), and the product was extracted with DCM (50 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, DCM/PE: gradient 1/20 to 1/1) to provide **12** (2.65 g, 93%) as a slightly brown solid, R_f = 0.4 (DCM/PE = 1/2). Mp = 62−64 °C; IR (KBr): 3286 (≡C−H), 3075, 2959, 2909, 2874, 2119 (C≡C), 1890, 1819, 1723 (C═O), 1684, 1606, 1587, 1459, 1415, 1378, 1344, 1321, 1322, 1298, 1248, 1208, 1168, 1103, 996, 952, 911, 891, 842 797, 766, 717, 702, 680, 651, 635 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 8.14 (d, J = 6.0 Hz, 2H), 4.1 (d, J = 6.8 Hz, 2H), 3.37 (s, 2H), 2.13−2.03 (m, 1H), 1.02 (d, 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K), δ = 167.7, 165.0, 164.3, 135.8, 126.92, 126.88, 111.87, 111.71, 84.22, 84.19, 75.4, 71.8, 28.0, 19.3; HRMS (EI-TOF) m/z: [M] calcd for $C_{15}H_{13}FO_2$ 244.0900; found 244.0903.

3,5-Dinitro-4-fluorobenzoic Acid (13). It was prepared according to the literature.[29] 4-Fluorobenzoic acid (9.0 g, 64.28 mmol) was added to oleum (28% SO_3, 60 mL) with stirring. To the solution was added 90% nitric acid (60 mL) dropwise, using an addition funnel, and the temperature was kept below 25 °C during the process. Then the solution was heated to 95 °C (reflux condenser attached). After 3 h, the mixture was cooled to room temperature and poured into ice/water, filtered by a vacuum, washed with cool water, and dried by vacuum at 50 °C to yield **13** (11.95 g, 81%) as a white solid, R_f = 0.2 (DCM/MeOH = 20/4). Mp 246−248 °C (lit.,[29] 238−240 °C); ^{1}H NMR (CD_3CN, 400 MHz, 298 K), δ = 8.84 (d, J = 6.0 Hz, 2H); ^{13}C NMR (CD_3COCD_3, 100 MHz, 298 K), δ = 163.6, 154.2, 151.4, 140.1, 132.4, 128.23, 128.19; MS (ESI) m/z: $[M - H]^-$ calcd for $C_7H_2FN_2O_6$ 229.0; found 229.0.

Isobutyl 3,5-Diamino-4-fluorobenzoate (15). Compound **13** (2.30 g 10.0 mmol) was suspended in DCM (30 mL, dry) under Ar, and oxalyl dichloride (1.70 mL, 20.0 mmol) and DMF (0.1 mL) were added. The mixture was stirred for 2 h, at room temperatue. The solvent and surplus oxalyl dichloride were removed under reduced pressure to yield the acid chloride, which was dried under vacuum for an additional 2 h. To a solution of isobutanol (0.92 mL, 10.0 mmol) in DCM (20 mL) containing *N*-ethyldiisopropylamine (1.72 mL, 10.0 mmol) was added the solution of acide chloride in DCM (20 mL) at 0 °C under Ar. The mixture was stirred overnight. When the reaction solution was exposed to air, the brown solution became dark brown slowly. Solvents were removed under reduced pressure to give crude product isobutyl 3,5-dinitro-4-fluorobenzoate (**14**). It is unstable and was used for the next step at once without purification. Compound **14** was dissolved in glacial acetic acid (80 mL), and the solution was heated. After the temperature rose to 90 °C, iron powder (5.6 g, 100.0 mmol) was added, and the mixture was heated to reflux for 5 h. When the mixture was cooled to room temperature, it was filtered. The filtrate was poured into water and extracted with ethyl acetate (30 mL × 5). The combined organic fractions were washed with brine (100 mL × 5), dried over Na_2SO_4, and filtered. Solvents were removed under reduced pressure, and the product was purified by flash chromatography (SiO_2, gradient DCM/PE to DCM/ethyl acetate = gradient 1/1 to 10/1) to yield **15** (1.40 g, 61%) as a brown solid, R_f = 0.2 (DCM/PE = 10/1). Mp = 72−73 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 6.91 (d, J = 8.0 Hz, 2H), 4.04 (d, J = 6.8 Hz, 2H), 3.75 (s, 4H), 2.09−1.99 (m, 1H), 1.0 (d, J = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K), δ = 166.5, 144.9, 142.5, 134.73, 134.62, 126.57, 126.54, 108.29, 108.26, 71.0, 27.9, 19.2; HRMS (ESI-FT-ICR) m/z: $[M + H]^+$ calcd for $C_{11}H_{16}FN_2O_2$ 227.1196; found 227.1191.

Isobutyl 3,5-Diazido-4-fluorobenzoate (16). Compound **15** (0.45 g, 2.0 mmol) was dissolved in dry THF (30 mL) under Ar and the solution was cooled to 0 °C with an ice/water bath. To the solution were added *tert*-butyl nitrite (0.47 mL, 4.0 mmol) and TFA (4 mL). The mixture was stirred for 0.5 h at 0 °C. A solution of sodium azide (0.52 g, 8.0 mmol) in H_2O (6 mL) was added slowly. The mixture was stirred at room temperature for 2 h and poured into water. The crude product was extracted with DCM (20 mL × 3). The combined organic layers were washed by brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, DCM/PE: gradient 1/20 to 2/10) to yield **16** (0.4 g, 72%) as a brown oil, R_f = 0.6 (DCM/PE = 2/1). IR (KBr): 3058, 2966, 2877, 2125 (N_3), 1726 (C═O), 1611, 1499, 1469, 1427, 1397, 1378, 1357, 1272, 1150, 1100, 994, 948, 886, 800, 764, 679, 654 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 7.54 (d, J = 6.8 Hz, 2H), 4.12 (d, J = 6.4 Hz, 2H), 2.12−2.05 (m, 1H), 1.01(d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K), δ = 164.2, 150.7, 148.1, 129.94, 129.84, 127.67, 127.63, 118.0, 71.8, 27.9, 19.1; HRMS (ESI-FT-ICR) m/z: $[M + Na]^+$ calcd for $C_{11}H_{11}FN_6O_2Na$ 301.0825; found 301.0824.

Trimer 17. Compound **16** (0.22 g, 0.79 mmol) and compound **12** (2.0 g, 8.20 mmol) were dissolved in a mixture of toluene (20 mL) and *tert*-butanol (20 mL) and then were degassed with argon. After 30 min, to the solution were added in sequence $CuSO_4$ (40.01 mg, 0.25 mmol) dissolved in water (2 mL) and sodium ascorbate (99.32 mg, 0.50 mmol) dissolved in water (2 mL). The mixture was stirred for 2 days at 90 °C with protection from light. The solvents were removed under reduced pressure, and the residue was redissolved in DCM, washed with saturated NH_4Cl (50 mL) and brine (50 mL), respectively, and then dried over Na_2SO_4. Solvents were removed under reduced

dx.doi.org/10.1021/jo500582c | J. Org. Chem. 2014, 79, 5134−5144

pressure, and the crude product was purified by flash chromatography (SiO_2, gradient DCM/PE to DCM/ethyl acetate = gradient 1/10 to 10/1) to yield **17** (0.33 g, 55%) as a pale solid, R_f = 0.4 (DCM/ethyl acetate = 30/1). Mp = 117−119 °C; IR (KBr): 3263 (≡C−H), 3087, 2964, 2883, 2117 (C≡C), 1724 (C═O), 1616, 1552, 1477, 1407, 1378, 1280, 1240, 1179, 1104, 1032, 989, 915, 819, 765, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 9.07 (dd, J = 2.4, 6.8 Hz, 2H), 8.81 (d, J = 6.8 Hz, 2H), 8.6 (t, J = 2.8 Hz, 2H), 8.22 (dd, J = 2.4 Hz, 6.8 Hz, 4H), 4.21 (d, J = 6.8 Hz, 2H), 4.16 (d, J = 6.8 Hz, 4H), 3.41 (s, 2H), 2,18−2.11 (m, 3H), 1.05 (d, J = 6.8 Hz, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K), δ = 164.8, 163.5, 163.4, 160.9, 149.0, 146.4, 141.1, 135.4, 130.14, 130.09, 129.24, 129.20, 127.73, 127.70, 126.83, 126.73, 126.47, 124.20, 124.12, 124.07, 123.99, 118.64, 118.50, 112.11, 111.94, 84.13, 84.10, 75.8, 72.6, 71.8, 28.02, 27.98, 19.36, 19.30; HRMS (MALDI-FT-ICR) m/z: $[M + H]^+$ calcd for $C_{41}H_{38}F_3N_6O_6$ 767.2805; found 767.2772.

3,5-Diiodo-4-chlorobenzoic Acid (18). Compound **18** was obtained by a similar procedure to compound **9** starting with 4-chlorobenzoic acid. Yield 76%, white solid. It was used without further purification, R_f = 0.2 (DCM/MeOH = 20/3). Mp > 300 °C (lit.,[28a] 288−290 °C); ^1H NMR (CD_3SOCD_3, 400 MHz, 298 K), δ = 13.59 (s, 1H), 8.35 (s, 2H); ^{13}C NMR (CD_3SOCD_3, 100 MHz, 298 K), δ = 164.1, 145.1, 140.3, 131.8, 98.4; HRMS (ESI-FT-ICR) m/z: $[M - H]^-$ calcd for $C_7H_2ClI_2O_2$ 406.7833; found 406.7825.

Isobutyl 3,5-Diiodo-4-chlorobenzoate (19). Compound **19** was obtained by a procedure similar to that for compound **8**, starting with compound **18**. Yield 84%, yellow solid, R_f = 0.5 (DCM/PE = 2/5). Mp = 131−132 °C; ^1H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 8.46 (s, 2H), 4.1 (d, J = 6.8 Hz, 2H), 2.11−2.04 (m, 1H), 1.01 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K), δ = 163.2, 146.6, 141.1, 131.1, 96.5, 72.0, 27.9, 19.3; HRMS (ESI-FT-ICR) m/z: $[M + Na]^+$ calcd for $C_{11}H_{11}ClI_2O_2Na$ 486.8435; found 486.8430.

Isobutyl 3,5-Ditrimethylsilylethynyl-4-chlorobenzoate (20). Compound **20** was obtained by a procedure similar to that for compound **11**, starting with compound **19**. Yield 76%, slightly yellow solid, R_f = 0.6 (DCM/PE = 1/2). Mp = 74−76 °C; IR (KBr): 2962, 2900, 2159 (C≡C), 1723 (C═O), 1637, 1568, 1544, 1468, 1403, 1378, 1344, 1321, 1248, 1229, 1124, 1063, 1002, 949, 907, 846, 764, 726, 702, 651 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 8.06 (s, 2H), 4.10 (d, J = 6.4 Hz, 2H), 2.13−2.03 (m, 1H), 1.01 (d, J = 6.8 Hz, 6H), 0.28 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K), δ = 164.8, 142.5, 133.9, 128.8, 124.2, 102.0, 100.3, 71.7, 28.0, 19.3, −0.1; HRMS (ESI-FT-ICR) m/z: $[M + H]^+$ calcd for $C_{21}H_{30}ClO_2Si_2$ 405.1473; found 405.1474.

Isobutyl 3,5-Diethynyl-4-chlorobenzoate (21). Compound **21** was obtained by a procedure similar to that for compound **12**, starting with compound **20**. Yield 93%, slightly brown solid, R_f = 0.4 (DCM/PE = 1/2). Mp = 76−77 °C; IR (KBr): 3291, 3253 (≡C−H), 3072, 2963, 2932, 2891, 2876, 2110 (C≡C), 1821, 1713 (C═O), 1574, 1544, 1469, 1399, 1377, 1340, 1314, 1261, 1231, 1129, 1105, 1061, 994, 946, 910, 804, 766, 704, 676, 644, 613 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 8.15 (s, 2H), 4.11 (d, J = 6.8 Hz, 2H), 3.45 (s, 2H), 2.12−2.05 (m, 1H), 1.02 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K), δ = 164.5, 142.7, 134.7, 129.1, 123.4, 84.0, 79.2, 71.8, 27.9, 19.3; HRMS (ESI-FT-ICR) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}ClO_2$ 261.0682; found 261.0676.

3,5-Dinitro-4-chlorobenzoic Acid (22). According to the literature[30a] 4-chlorobenzoic acid (5.0 g, 32.05 mmol) was dissolved in concentrated H_2SO_4 (50 mL). To the solution was added KNO_3 (8.1 g, 80.2 mmol) in batches, and the temperature was kept below 40 °C during the process. The mixture was heated to 140 °C and stirred for 5 h (reflux condenser attached). It was cooled to room temperature and poured into ice/water, filtered, washed with cool water, and dried by vacuum to yield **22** (7.2 g, 91%) as a white solid, R_f = 0.5 (DCM/MeOH = 20/5). Mp = 165−167 °C (lit.,[30b] 161−163 °C); ^1H NMR (CD_3SOCD_3, 400 MHz, 298 K), δ = 14.27 (b, 1H), 8.77 (s, 2H); ^{13}C NMR (CD_3COCD_3, 100 MHz, 298 K), δ = 163.6, 150.5, 132.8, 129.4, 124.3.

Isobutyl 3,5-Dinitro-4-chlorobenzoate (23). Compound **23** was obtained by a procedure similar to that for compound **8**, starting with compound **22**. Yield 98%, yellow solid, R_f = 0.5 (DCM/PE = 1/2). Mp = 95−96 °C; IR (KBr): 3083, 2969, 1721 (C═O), 1611, 1546, 1469, 1359, 1307, 1188, 1136, 1065, 984, 933, 781, 752, 718 cm-^{1}; H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 8.58 (s, 2H), 4.20 (d, J = 6.8 Hz, 2H), 2.17−2.07 (m, 1H), 1.02 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K), δ = 162.0, 149.8, 131.4, 128.21, 128.05, 124.7, 73.0, 27.9, 19.2.

Isobutyl 5-Nitro-3-amino-4-chlorobenzoate (24). To a mixture of glacial acetic acid (30 mL) and methanol (30 mL) was added compound **23** (4.0 g, 13.24 mmol). After the mixture was heated to 70 °C, reduced iron powder (2.22 g, 39.73 mmol) was added in six times. The reaction was monitored by TLC. When the starting material vanished, the mixture was cooled to room temperature and filtered. The filtrate was poured into water and extracted with ethyl acetate (30 mL × 5). The combined organic fractions were washed with brine (100 mL × 5), dried over Na_2SO_4, and filtered. Solvents were removed under reduced pressure, and the residue was dried by vacuum to give crude **24** (2.44 g, 67%) as a brown-black solid, which was used without further purification. Pure **24** was recrystallized from DCM and PE, R_f = 0.5 (DCM/PE = 20/3). Mp = 88−89 °C; ^1H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 7.79 (d, J = 1.6 Hz, 1H,), 7.6 (d, J = 1.6 Hz, 1H), 4.56 (s, 2H), 4.11 (d, J = 6.8 Hz, 2H), 2.11−2.05 (m, 1H), 1.01 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K), δ = 164.4, 149.2, 145.3, 130.1, 118.7, 114.57, 114.51, 72.0, 27.9, 19.2; HRMS (ESI-FT-ICR) m/z: $[M + H]^+$ calcd for $C_{11}H_{14}ClN_2O_4$ 273.0642; found 273.0639.

Isobutyl 5-Nitro-3-azido-4-chlorobenzoate (25). Compound **25** was obtained by a procedure to similar to that for compound **7**, starting with compound **24**. Yield 90%, white solid, R_f = 0.6 (DCM/PE = 1/2). Mp = 83−84 °C; IR (KBr): 3078, 2982, 2963, 2936, 2895, 2878, 2139 (N_3), 2100, 1827, 1721 (C═O), 1682, 1658, 1594, 1576, 1548, 1467, 1400, 1375, 1319, 1275, 1212, 1170, 1137, 1108, 1063, 992, 933, 918, 826, 890, 790, 768, 722, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 8.15 (d, J = 1.6 Hz, 1H), 8.02(d, J = 1.6 Hz, 1H), 4.17 (d, J = 6.8 Hz, 2H), 2.17−2.07 (m, 1H), 1.02 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K): δ = 163.3, 149.9, 140.8, 130.7, 122.66, 122.20, 121.26, 72.5, 27.9, 19.2; HRMS (ESI-FT-ICR) m/z: $[M + Na]^+$ calcd for $C_{11}H_{11}ClN_4O_4Na$ 321.0367; found 321.0363.

Isobutyl 5-Nitro-3-(tertbutylcarbonyl)amino-4-chlorobenzoate (26). To a solution of compound **24** (0.59 g, 2.17 mmol) and *N*-ethyldiisopropylamine (0.41 mL, 2.39 mmol) in dry DCM (20 mL) under N_2 was added pivaloyl chloride (0.29 mL, 2.38 mmol) dropwise at 0 °C. The mixture was stirred overnight at room temperature. Solvent was removed under reduced pressure, and the residue was purified by flash chromatography (SiO_2, DCM/PE = gradient 1/20 to 1/1) to provide **26** (0.73 g, 95%) of yellow solid, R_f = 0.6 (DCM/PE = 10/1). Mp = 99−100 °C;. ^1H NMR ($CDCl_3$ 400 MHz, 298 K): δ = 9.3 (d, J = 1.6 Hz, 1H), 8.2 (d, J = 1.6 Hz, 2H), 4.15 (d, J = 6.8 Hz, 2H), 2.15−2.08 (m, 1H), 1.38 (s, 9H), 1.02 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$ 100 MHz, 298 K): δ = 176.9, 163.9, 148.4, 137.2, 130.8, 125.1, 120.4, 119.4, 72.2, 40.6, 27.93, 27.58, 19.2. HRMS (ESI-FT-ICR) m/z: $[M + H]^+$ calcd for $C_{16}H_{22}ClN_2O_5$ 357.1217; found 357.1211.

Isobutyl 5-Amino-3-(*tert*-butylcarbonyl)amino-4-chlorobenzoate (27). To the solution of **26** (1.0 g, 2.81 mmol) in ethyl acetate (50 mL) was added Pd/C (0.1 g, 10%). The mixture was stirred overnight in hydrogen atmosphere at room temperature. It was filtered through Celite. The solvent was removed under reduced pressure and the residue was dried to yield **27** (0.90 g, 98%) as a yellow solid, R_f = 0.3 (DCM/ethyl acetate =30/1). Mp = 123−125 °C; ^1H NMR ($CDCl_3$ 400 MHz, 298 K): δ = 8.43 (d, J = 1.6 Hz, 1H), 7.94 (s, 1H), 7.24 (d, J = 1.6 Hz, 1H), 4.16(s, 2H), 4.08 (d, J = 6.8 Hz, 2H), 2.11−2.05 (m, 1H), 1.36 (s, 9H), 1.01 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$ 100 MHz, 298 K): δ = 176.6, 166.2, 143.1, 135.4, 130.2, 113.0, 112.05, 112.01, 71.4, 40.4, 28.0, 27.74, 19.4; HRMS (ESI-FT-ICR) m/z: $[M + H]^+$ calcd for $C_{16}H_{24}ClN_2O_3$ 327.1475; found 327.1468.

Isobutyl 5Azido-3-(*tert*-butylcarbonyl)amino-4-chlorobenzoate (28). Compound **28** was obtained by a procedure similar to

dx.doi.org/10.1021/jo500582c | J. Org. Chem. 2014, 79, 5134−5144

that for compound **7**, starting with compound **27**. Yield 95%, white solid, R_f = 0.3 (DCM/PE = 2/1). Mp = 143−145 °C; IR (KBr): 3118, 2969, 2874, 2118 (N_3), 1713 (C═O), 1673, 1589, 1536, 1469, 1430, 1399, 1381, 1350, 1302, 1266, 1244, 1195, 1161, 1123, 1050, 1002, 977, 901, 869, 762, 733, 647 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 8.88 (d, J = 1.6 Hz, 1H), 8.08 (s, 1H), 7.63 (d, J = 1.6, 1H Hz), 4.12 (d, J = 6.8 Hz, 2H), 2.15−2.08 (m, 1H), 1.36 (s, 9H), 1.01 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$ 100 MHz, 298 K): δ = 176.8, 165.2, 138.1, 136.7, 130.7, 118.00, 117.83, 114.9, 71.8, 40.5, 28.00, 27.66, 19.3. HRMS (ESI-FT-ICR) m/z: $[M + H]^+$ calcd for $C_{16}H_{22}ClN_4O_3$ 353.1380; found 353.1372.

Trimer 1. Compound **8** (0.35 g, 1.47 mmol) and compound **12** (0.12 g, 0.49 mmol) were dissolved in the mixture of toluene (10 mL) and *tert*-butanol (10 mL) and then were degassed with argon. After 30 min, to the solution were added in sequence $CuSO_4$ (23 mg, 0.14 mmol) dissolved in water (1 mL) and sodium ascorbate (59 mg, 0.29 mmol) dissolved in water (1 mL). The mixture was stirred at 90 °C overnight with protection from light. Solvents were removed under reduced pressure, and the residue was redissolved in DCM, washed with saturated NH_4Cl (50 mL) and brine (50 mL × 2), dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by flash chromatography (SiO_2, gradient DCM/PE to DCM/ethyl acetate = gradient 1/1 to 10/1) to yield **1** (0.29 g, 83%) as a white solid, R_f = 0.6 (DCM/ethyl acetate = 30/1). Mp = 169−170 °C; ^1H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 9.07 (d, J = 6.8, 2H), 8.74 (dd, J = 2.0 Hz, 7.2 Hz, 2H), 8.58 (t, J = 3.0 Hz, 2H), 8.22−8.18 (m, 2H), 7.44 (dd, J = 8.8 Hz, 10.3 Hz, 2H), 4.20 (d, J = 6.8 Hz, 2H), 4.16 (d, J = 6.8 Hz, 4H), 2.20−2.07 (m, 3H), 1.07 (d, J = 6.8 Hz, 6H), 1.04 (d, J = 6.8 Hz, 12H); ^{13}C NMR ($CDCl_3$, 150 MHz, 298 K), δ = 165.2, 164.4, 159.0, 157.3, 156.9, 155.2, 141.0, 131.95, 131.90, 129.47, 128.35, 128.12, 126.6, 125.19, 125.12, 123.9, 119.09, 118.99, 117.46, 117.32, 71.80, 71.60, 53.4, 30.9, 27.91, 27.87, 19.30, 19.18; HRMS (ESI-FT-ICR) m/z: $[M + H]^+$ calcd for $C_{37}H_{38}F_3N_6O_6$ 719.2805; found 719.2819.

Pentamer 2. Compound **8** (0.27 g, 1.14 mmol), compound **17** (0.3 g, 0.39 mmol), and tris(benzyltriazolylmethyl)amine (34.03 mg, 0.06 mmol) were dissolved in the mixture of toluene (15 mL) and *tert*-butanol (15 mL) and then were degassed with argon. After 30 min, to the solution were added $CuSO_4$ (18.92 mg, 0.12 mmol) dissolved in water (1 mL) and sodium ascorbate (46.61 mg, 0.24 mmol) dissolved in water (1 mL). The mixture was stirred at 90 °C for 5 days with protection from light. The solvents were removed in vacuo, and the residue was redissolved in DCM, washed with saturated NH_4Cl (50 mL) and brine (50 mL), respectively, and dried over Na_2SO_4. Solvents were evaporated, and the crude was purified by flash chromatography (SiO_2, gradient DCM/PE to DCM/ethyl acetate = gradient 1/1 to 10/3) to yield **2** (0.25 g, 52%) as a white solid, R_f = 0.2 (DCM/ethyl acetate = 20/1). Mp = 229−231 °C; ^1H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 9.08−9.07 (m, 4H), 8.83 (d, J = 6.4 Hz, 2H), 8.74 (dd, J = 2.0 Hz, 7.2 Hz, 2H), 8.66 (t, J = 2.8 Hz, 2H), 8.57 (t, J = 3.0 Hz, 2H), 8.20−8.16 (m, 2H), 7.42 (dd, J = 8.8 Hz, 10.4 Hz), 4.24 (d, J = 6.4 Hz, 2H), 4.22 (d, J = 6.8 Hz, 4H), 4.16 (d, J = 6.8 Hz, 4H), 2.22−2.09 (m, 5H), 1.09−1.02 (m, 30H); ^{13}C NMR ($CDCl_3$, 125 MHz, 298 K), δ = 165.3, 164.5, 163.4, 159.3, 157.3, 157.1, 155.1, 148.9, 146.8, 141.6, 141.1, 132.09, 132.02, 129.89, 129.63, 129.25, 128.52, 128.49, 128.38, 126.87, 126.79, 126.65, 126.47, 125.27, 125.18, 124.06, 123.96, 119.31, 119.20, 118.86, 118.75, 117.59, 117.42, 72.6, 71.95, 71.80, 28.05, 27.98, 27.05, 19.42, 19.30;. HRMS (MALDI-FT-ICR) m/z: $[M + Na]^+$ calcd for $C_{63}H_{61}F_5N_{12}O_{10}Na$ 1263.4451; found 1263.4438.

Trimer 3. Compound **21** (52.8 mg, 0.20 mmol) and compound **25** (149.3 mg, 0.50 mmol) were dissolved in toluene (10 mL) and *tert*-butanol (10 mL) and degassed with argon. After 30 min, $CuSO_4$ (9.4 mg, 0.06 mmol) dissolved in water (1 mL) and sodium ascorbate (24.1 mg, 0.12 mmol) dissolved in water (1 mL) were added to the solution. The mixture was stirred overnight at 35 °C, protected from light. Solvents were removed under reduced pressure, and the residue was dissolved in DCM. The solution was washed with saturated NH_4Cl (50 mL) and brine (50 mL × 2), respectively, and dried over Na_2SO_4. Solvents were evaporated, and the product was purified by flash chromatography (SiO_2, gradient DCM/PE to DCM/ethyl acetate = gradient 1/1 to 10/1) to yield **3** (136.2 mg, 79%) as a white solid, R_f = 0.4 (DCM/ethyl acetate = 30/1). Mp = 192−194 °C; ^1H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 8.94 (s, 2H), 8.67 (s, 2H), 8.62 (d, J = 1.2 Hz, 2H), 8.58 (d, J = 1.2 Hz, 2H), 4.22−4.20 (m, 6H), 2.22−2.11 (m, 3H), 1.07 (d, J = 4.4 Hz, 6H), 1.06 (d, J = 4.4 Hz, 12H); ^{13}C NMR ($CDCl_3$, 150 MHz, 298 K), δ = 165.1, 162.6, 149.6, 144.1, 136.9, 133.4, 131.51, 131.45, 130.37, 126.9, 125.8, 72.8, 71.8, 27.98, 27.88, 19.33, 19.19; HRMS (ESI-FT-ICR) m/z: $[M + H]^+$ calcd for $C_{37}H_{36}Cl_3N_8O_{10}$ 857.1620; found 857.1606.

Trimer 4. Compound **21** (0.13 g, 0.5 mmol) and compound **28** (0.43 g, 1.22 mmol) were dissolved in toluene (10 mL) and *tert*-butanol (10 mL) and degassed with argon. After 30 min, $CuSO_4$ (16.1 mg, 0.1 mmol) dissolved in water (1 mL) and sodium ascorbate (39.8 mg, 0.2 mmol) dissolved in water (1 mL) were added to the solution. The mixture was stirred overnight at 90 °C, protected from light. Solvents were removed under reduced pressure, and the residue was dissolved in DCM. The solution was washed with saturated NH_4Cl (50 mL) and brine (50 mL × 2), respectively, and dried over Na_2SO_4. Solvents were evaporated, and the product was purified by flash chromatography (SiO_2, gradient DCM/PE to DCM/ethyl acetate = gradient 1/1 to 10/1) to yield **4** (0.37 g, 77%) as a white solid, R_f = 0.4 (DCM/ethyl acetate = 30/4). Mp = 213−214 °C; ^1H NMR ($CDCl_3$, 400 MHz, 298 K), δ = 9.27 (d, J = 2.0 Hz, 2H), 8.93 (s, 2H), 8.51 (s, 2H), 8.14 (s, 2H), 8.06 (s, J = 2.0 Hz, 2H), 4.20 (d, J = 6.8 Hz, 2H), 4.16 (s, J = 6.8 Hz, 4H), 2.22−2.08 (m, 3H), 1.39 (s, 18H), 1.05 (d, J = 6.8 Hz, 6H), 1.02 (d, J = 6.8 Hz, 12H); ^{13}C NMR ($CDCl_3$, 150 MHz, 298 K), δ = 176.9, 165.4, 164.5, 143.9, 136.8, 135.0, 133.5, 131.40, 131.00, 130.73, 130.28, 125.7, 123.70, 123.42, 123.12, 72.07, 71.80, 40.6, 28.02, 27.96, 27.65, 19.39, 19.30; HRMS (ESI-FT-ICR) m/z: $[M + H]^+$ calcd for $C_{47}H_{56}Cl_3N_8O_8$ 965.3287; found 965.3255.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H NMR, ^{13}C NMR, and 2D NMR spectra and X-ray crystallographic data as well as computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21125205 and 21332008) for financial support. We also thank the Holland Computing Center at the University of Nebraska-Lincoln, for computational resources.

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